IB/2004/03238

PA 1233627

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

October 06, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *60/510,870*
FILING DATE: *October 14, 2003*

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. JACKSON
Certifying Officer

PTO/SB/16 (05-03)
Approved for use through 4/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 325048299 US

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Mark	Boys	Mt. Prospect, Illinois
Michael	Clare	Skokie, Illinois
Mark	Mitton-Fry	Clinton, Connecticut

☐ *Additional inventors are being named on th____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Substituted Pyrazinone Compounds for the Treatment of Inflammation

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☒ Customer Number **26648** → *Place Customer Number Bar Code Label here*

Type Customer Number here

OR

☐ Firm *or* Individual Name	
Address	
Address	

City		State		ZIP	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* **48**
☐ CD(s), Number
☐ Drawing(s) *Number of Sheets*
☐ Other (specify)
☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees
☒ The Director is hereby authorized to charge filling fees or credit any overpayment to Deposit Account Number **19-1025**
☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($) **$160.00**

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME **S. Christopher Bauer**

TELEPHONE **314-274-6257**

Date **10/14/03**

REGISTRATION NO. *(if appropriate)* **42,305**

Docket Number: **01710/1/PR**

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Provisional Application,**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/17 (5-03)
Approved for use through 04/30/2003. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) **$200.00**

Complete if Known	
Application Number	Not Assigned
Filing Date	October 14, 2003
First Named Inventor	M. Boys
Examiner Name	Not Assigned
Group Art Unit	Not Assigned
Attorney Docket No.	01710/1/PR

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: **19-1025**

Deposit Account Name: **Pharmacia Corporation**

The Commissioner is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing	
1005	160	2005	80	Provisional filing fee	160.00

SUBTOTAL (1) ($) **$160.00**

2. EXTRA CLAIM FEES FOR UTILITY AND

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** = 0	X	=	0.00
Independent Claims		- 3** = 0	X	=	0.00
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) **$0.00**

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non - English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR § 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Statement	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	40.00
1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) **$40.00**

SUBMITTED BY

Complete *(if applicable)*

Name (Print/Type)	E. Christopher Bauer	Registration No. (Attorney/Agent)	42,305	Telephone	314-274-6257
Signature				Date	October 14, 2003

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

SUBSTITUTED PYRAZINONE COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

[001] The present invention in general is in the field of anti-inflammatory pharmaceutical agents and specifically relates to substituted pyrazinone derivatives, compositions comprising such, and methods for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

[002] The following description of the background of the invention is provided to aid in the understanding the invention, but is not admitted to be or describe prior art to the invention.

[003] NF-κB is a ubiquitous transcription factor that plays a prominent role in the activation of the immune system and in stress responses by regulating the transcription of many early, inducible genes including proinflammatory cytokines, adhesion molecules, growth factors, enzymes, and receptors (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). Specificity of gene expression is determined at a cellular level by a diverse array of external stimuli such as bacterial products including LPS, as well as cytokines, most importantly tumor necrosis factor-α (TNFα) and interleukin-β (IL1β). Through the synergistic interaction with other transcription factors, further specificity can be achieved while maintaining enormous potential to coordinately induce a large number of functionally related genes. NF-κB is composed of homo and heterodimers of the Rel protein family and is sequestered in an inactive form in the cytoplasm by members of the IκB family of inhibitory proteins (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). IκBs mask the nuclear localization signal on NF-κB, preventing

nuclear translocation and hence DNA binding to the promoter regions of responsive genes. Stimulation of cells with an agonist that activates NF-κB leads to a series of biochemical signals, ultimately resulting in the phosphorylation, ubiquitinylation, and degradation of IκBs, thereby releasing NF-κB for nuclear translocation (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). Recently, two IκB kinases (IKK1 or IKKα and IKK2 or IKKβ), which phosphorylate IκBs and thereby initiate their degradation, have been cloned and characterized by a number of laboratories (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). The catalytic subunits, IKK1 and IKK2, are similar structurally as well as enzymatically and exist as a heterodimer in a large protein complex referred to as the IKK signalsome (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* 278, 866-869). A third protein, NEMO (IKKγ, IKKAP1), is a regulatory adapter protein necessary for IKK activation and kinase activity (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* 93, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* 395, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* 2, 1526-1538). IKK1 and IKK2 are co-expressed in most human adult tissues as well as in different developmental stages of mouse embryos (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M.,

Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* 278, 866-869; Hu, M. C. T., and Wang, Y. (1998) *Gene* 222, 31-40). This kinase complex appears to represent a critical, common denominator in the activation of NF-κB in a number of signal transduction pathways stimulated by a variety of agonists including cytokines, such as TNFα and IL1β, microbial products such as LPS and viral proteins such as TAX, as well as phorbol esters, oxidizing agents and serine/tyrosine phosphatases (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342).

[004] IKK1 (also termed IKKα, Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. And Roa, A. (1997) *Science* 278, 860-866) was cloned simultaneously by standard biochemical purification of the IκB kinase activity from TNFα stimulated HeLa S3 cells and by its interaction with the MAP3K, NF-κB inducing kinase (NIK), in a yeast two-hybrid screen. IKK1 was identified as the previously cloned serine-threonine kinase, CHUK (Connelly, M. and Marcu, K. (1995) *Cell. Mol. Biol. Res.* 41, 537-549). IKK1 (also termed IKKα) is an 85 kDa, 745 amino acid protein that contains an N-terminal serine/threonine kinase catalytic domain, a leucine zipper-like amphipathic helix, and a C-terminal helix-loop-helix domain. IKK2 (also termed IKKβ) was also cloned by standard biochemical purification, copurifying with IKK1 from TNFα stimulated HeLa S3 cells as well as by being identified in the public database from an EST clone with sequence homology to IKK1 (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* 278, 866-869). IKK2 is an 87 kDa, 756 amino acid protein with the same over all

topology as IKK1 except for the addition of an 11 amino acid extension at the C-terminus. IKK1 and IKK2 are 52% identical overall with 65% identity in the kinase domain and 44% identity in the protein interaction domains in the C-terminus. Data obtained using transient mammalian expression analysis, by *in vitro* translation experiments and by coexpression in a baculoviral system reveals that IKK1 and IKK2 associate preferentially as a heterodimer through their leucine zipper motifs. Although homodimers have also been described in these systems, the heterodimer is thought to be the physiologic form of the kinase in mammalian cells (Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Li, J., Peet, G.W., Pullen, S.S., Schembri-King, J., Warren, T.C., Marcu, K.B., Kehry, M.R., Barton, R. and Jakes, S. (1998) *J. Biol. Chem.* 273, 30736-30741). Finally, NEMO (also termed IKKγ) contains three α-helical regions including a leucine zipper, interacts preferentially with IKK2 and is required for activation of the heterodimeric kinase complex perhaps by bringing other proteins into the signalsome complex (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* 93, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* 395, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* 2, 1526-1538).

[005] The kinase activities of IKK1 and IKK2 are regulated by phosphorylation and require an intact leucine zipper (LZ) for dimerization as well as an intact helix-loop-helix (HLH) domain, which can exert a positive regulatory effect on kinase activity even when it is expressed in trans with the remainder of the IKK protein (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio,F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* 278, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313).

Both IKK subunits contain a canonical MAPKK activation loop motif near the N-terminus which is the target for phosphorylation and activation of kinase activity by MAP3Ks such as NIK and MEKK1, although the physiologic regulation by these two upstream kinases awaits further characterization (Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342; Karin, M., and Delhase, M. (1998) *Proc. Natl. Acad. Sci.* USA 95, 9067-9069). Finally, phosphorylation of serines in the C-terminus of IKK2 results in a decrease in IKK activity and it is postulated to be responsible for the transient kinase activity seen after stimulation of cells with an agonist (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313).

[006] IKK2 demonstrates a more potent kinase activity compared to IKK1 using IκBα or IκBβ as a substrate (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* 278, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313). Mutations of the phospho-acceptor serine residues within the MAPKK activation loop alters IKK2 kinase activity; the serine to alanine substitutions result in decreased kinase activity whereas the serine to glutamic acid substitutions result in a constitutively active kinase. Similar alanine mutations in IKK1 do not result in a decreased stimulation of total IKK activity in response to TNFα or IL1β (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313). IKK2 being the dominant kinase activity within the IKK complex is further supported by the analysis of fibroblasts from mice deficient in IKK1 or IKK2. Fibroblasts lacking IKK1 retain full IKK activity in response to cytokines and could activate NF-κB. In contrast, fibroblasts lacking IKK2 do not exhibit IKK activity when stimulated with cytokines nor do they activate NF-κB. Furthermore, the phenotypes of each IKK knock out is unique with IKK1 deficiency resulting in skin and skeletal defects and IKK2 knock out being embryonic lethal due to hepatocyte apoptosis (Li, Q., Antwerp, D. V., Mercurio, F., Lee, K., and Verma, I. M. (1999) *Science* 284, 321-325; Takeda, K., Tekeuchi, O., Tsujimura, T., Itami, S., Adachi, O.,

Kawai, T., Sanjo, H., Yoshikawa, K., Terada, N, and Akira, S. (1999) *Science* 284, 313-316; Hu, Y., Baud, V., Delhase, M., Zhang, P., Deerinck, T., Ellisman, M., Johnson, R., and Karin, M. (1999) *Science* 284, 315-320; Li, Q., Lu, Q., Hwang, J. Y., Buscher, D., Lee, K., Izpisua-Belmonte, J. C., and Verma, I. M. (1999) *Gene and Development* 13, 1322-1328; Tanaka, M., Fuentes, M. E., Yamaguchi, K., Durnin, M. H., Dalrymple, S. A., Hardy, K. L., and Goeddel, D. V. (1999) *Immunity* 10, 421-429).

[007] It is well-known that NF-κB plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as IL-6 and IL-8, cell adhesion molecules, such as ICAM and VCAM, and inducible nitric oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases. The importance of NF-κB in inflammatory disorders is further strengthened by studies of airway inflammation including asthma in which NF-κB has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyperresponsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF-κB, one may speculate that these effects are mediated through an inhibition of NF-κB. Further evidence for a role of NF-κB in inflammatory disorders comes from studies of rheumatoid synovium. Although NF-κB is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF-κB is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF-κB has been shown to be activated in human synovial cells in response to stimulation with TNF-α. Such a distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., J. Biol. Chem., 271, 31496-31501 (1996).

[008] The NF-κB/Rel and IκB proteins are also likely to play a key role in neoplastic transformation. Family members are associated with cell transformation in vitro and in vivo because of overexpression, gene amplification, gene

rearrangements, or translocations (Gilmore TD, *Trends Genet* 7:318-322, 1991; Gillmore TD, *Oncogene* 18:6925-6937, 1999; Rayet B. et al., *Oncogene* 18: 6938-6947, 1991). In addition, rearrangement and/or amplification of the genes encoding these proteins are seen in 20-25% of certain human lymphoid tumors. In addition, a role for NF-κB in the regulation of apoptosis, cell cycle progression, invasion, and metastasis has been reported (Bours V. et al., *Biochemical Pharmacology* 60:1085-1090, 2000) strengthening the role of this transcription factor in the control of cell proliferation. The inhibition of NF-κB has been shown to potentiate TNF- and cancer therapy through increased apoptosis (Wang C-Y et al., *Science* 274:784-787, 1996; Wang C-Y et al., *Nat Med* 5:412-417, 1999). It has also been shown that human T-cell leukemia virus type 1 (HTLV1) infected cells (the etiological agent of an aggressive malignancy of activated $CD4^+$ T lymphocytes), IKKα and IKKβ are expressed constitutively, which normally function in a transient manner (Chu Z-L et al., *J of Biological Chemistry* 273:15891-15894, 1998). The HTLV1 transforming and transactivating protein (Tax) has been shown to bind MEKK1 and increases the activity of IKKβ to enhance phosphorylation of serine residues in IκBα that lead to its degradation.

[009] Some substituted pyrazines, pyrimidines and pyridazines useful for the treatment of senile dementia as described in US 5,260,293.

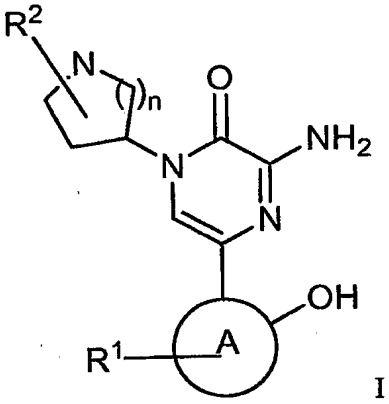
[0010] WO 01/05772 discloses substituted pyrazinones as caspase-3 inhibitors.

[0011] Diaryl piperazines and related compounds as selective modulators of capsaicin receptors are disclosed in WO 02/08221.

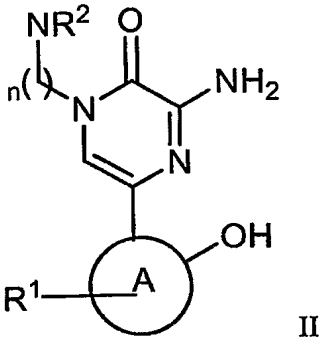
[0012] Pyrazinones and triazinones and derivatives thereof are disclosed for the treatment of psychiatric disorders and neurological diseases in WO 98/11075.

DETAILED DESCRIPTION OF THE INVENTION

[0013] A class of compounds, which are useful in treating cancer, inflammation, and inflammation related disorders, is defined by Formula I and II



I



II

wherein

n is 1, 2, or 3

A is a 3 to 12 membered fused or unfused heteroaryl or aryl, optionally saturated, and optionally substituted with one or more R^1 group;

$\mathbf{R^1}$ is independently selected from the group consisting of: hydrido, halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, alkenyl, OR^3, $(CH_2)_mOR^3$ wherein m is 1, 2, or 3, $(CH_2)_pCO_2R^3$ wherein p is 1, or 2, SR^4, $SO_2N(R^4)\,R^{4'}$, NHR^5, $NHCOR^5$, NR^5COR^5, $NHCO(OR^5)$, $NR^5CO(OR^5)$, $NR^5SO_2R^6$, $NHSO_2N(R^6)R^{6'}$, $NR^5CON(R^6)R^{6'}$, COR^5, CO_2R^4, $CON(R^4)\,R^{4'}$, wherein R^4 and $R^{4'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, wherein R^6 and $R^{6'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, and wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^5;

$\mathbf{R^2}$ is one or more substituent independently selected from the group consisting of: hydrido, halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, alkenyl, OR^3, SR^4, $SO_2N(R^4)\,R^{4'}$, NHR^5, $NHCOR^5$, NR^5COR^5, $NHCO(OR^5)$, $NR^5CO(OR^5)$, $NR^5SO_2R^6$, $NHSO_2N(R^6)R^{6'}$, $NR^5CON(R^6)R^{6'}$, COR^5, CO_2R^4, $CON(R^4)\,R^{4'}$, wherein R^4 and $R^{4'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms

selected from S, SO, SO_2, O, N, and NR^5, wherein R^6 and $R^{6'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, and wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^5;

R^3 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, heteroarylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, heterocyclic, cycloalkyl, cycloalkylalkyl, arylalkyl, and arylalkylamino wherein said aryl is optionally substituted wit one or more radical selected from the group consisting of lower alkyl, aminoalkyl, alkoxy and halogen;

R^4 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, heteroarylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, heterocyclic, cycloalkyl, cycloalkylalkyl, arylalkyl, and arylalkylamino wherein said aryl is optionally substituted wit one or more radical selected from the group consisting of lower alkyl, aminoalkyl, alkoxy and halogen;

$R^{4'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, heteroarylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, heterocyclic, cycloalkyl, cycloalkylalkyl, arylalkyl, and arylalkylamino wherein said aryl is optionally substituted wit one or more radical selected from the group consisting of lower alkyl, aminoalkyl, alkoxy and halogen;

R^5 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl,

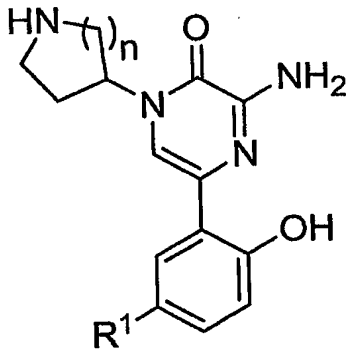
alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^6 is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic; and

$R^{6'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

or isomers, tautomers, polymorphs, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

[0014] Specific embodiments of the invention are compounds of formula III, IV, V, VI, VII and VIII.



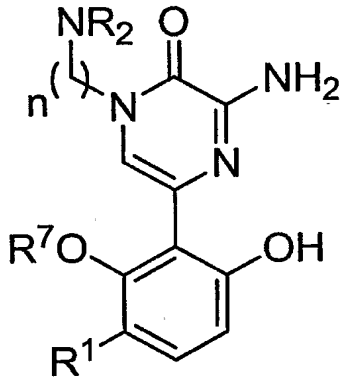
III

wherein

n is 1, 2, or 3;

R^1 is selected from the group consisiting of hydrido, OR^3, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, and heterocyclic; and

R^3 is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl.



IV

wherein

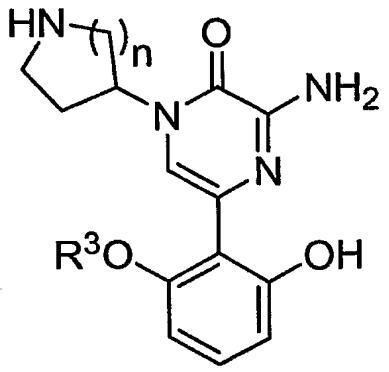
n is 1, 2, or 3;

R^2 is hydrido or lower alkyl;

R^1 is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, OR^3 and heterocyclic;

R^3 is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl; and

R^7 is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7cycloalkyl, CH_2C_3-C_7cycloalkyl, and benzyl.

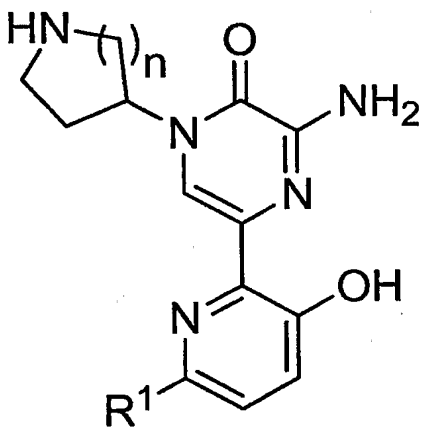


V

wherein

n is 1, 2, or 3; and

$\mathbf{R^3}$ is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, CH_2C_3-C_7 cycloalkyl, and benzyl.



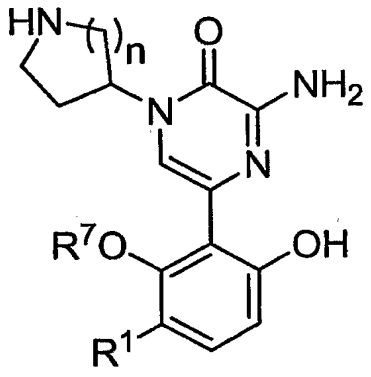
VI

wherein

n is 1, 2, or 3;

$\mathbf{R^1}$ is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, OR^3 and heterocyclic; and

$\mathbf{R^3}$ is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl.



VII

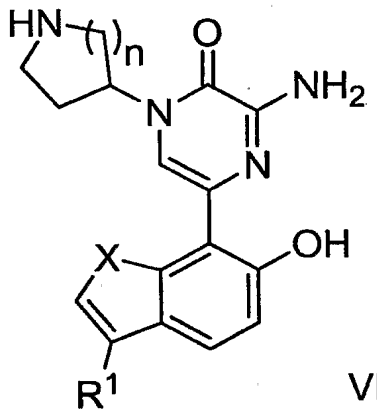
wherein

n is 1, 2, or 3;

R^1 is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, OR^3 and heterocyclic;

R^3 is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl; and

R^7 is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and benzyl.



VIII

wherein

n is 1, 2, or 3;

X is S or O;

R^1 is $(CH_2)_mOR^3$ or $(CH_2)_pCO_2R^3$;

m is 1, 2, or 3;

p is 0, 1, or 2; and

R^3 is hydrido or C_1-C_6 alkyl.

Definitions

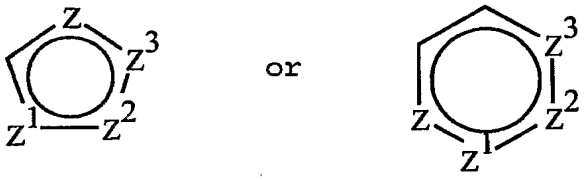
[0015] The present invention includes the use of all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which releases the active parent drug according to Formula I or II in vivo. If a chiral center or another form of an isomeric center is present in a compound of the present invention all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein.

Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0016] The meaning of any substituent at any one occurrence in Formula I, II or any sub-Formula thereof is independent of its meaning, or any other substituents meaning, at any other occurrence, unless specified otherwise.

[0017] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxylradicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or

branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclic" or "heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms can be replaced by N, S, P, or O. This includes, for example, the following structures:



wherein Z, Z^1, Z^2 or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2 or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2 or Z^3 only when each is C.

[0018] "Heterocyclic" in cludes, furanyl, thienyl, pyrrolyl, 2-isopyrrolyl, 3-isopyrrolyl, pyrazolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyranonyl, 1,4-pyranonyl, 1,2-dioxinyl, 1,3-dioxinyl, pyridyl,

pyridazyl, pyrimidyl, pyrazinyl, piperazyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiainzyl, 1,2,6-oxathiainzyl, 1,4,2-oxadiainzyl, 1,3,5,2-oxadiainzyl, morpholino, azepinyl, oxepinyl, thiepinyl, 1,2,4-diazepinyl, benzofuranyl, isobenzofuranyl, benzothiofuranyl, isobenzothiofuranyl, indolyl, indoleninyl, 2-isobenzazolyl, 1,5-pyrindinyl, pyrano[3,4-b]pyrrolyl, isoindazolyl, indoxazinyl, benzoxazolyl, anthranilyl, 1,2-benzopyranyl, quinolyl, isoquinolyl, cinnolyl, quinazolyl, naphthyridyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, 1,3,2-benzoxazyl, 1,4,2-benzoxazyl, 2,1,3-benzoxazyl, 3,1,4-benzoxazyl, 1,2-benzoisoxazyl, 1,4-benzoisoxazyl, carbazolyl, xanthenyl, acridinyl, purinyl, thiazolidyl, piperidyl, pyrrolidyl, 1,2-dihydroazinyl, 1,4-dihydroazinyl, 1,2,3,6-tetrahydro-1,3-diazinyl, perhydro-1,4-diazinyl, 1,2-thiapyranyl, and 1,4-thiapyranyl. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include furanyl, thienyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2-pyranonyl, 1,4-pyranonyl, pyridyl, pyridazyl, pyrimidyl, piperazyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuranyl, isobenzofuranyl, benzothiofuranyl, isobenzothiofuranyl, indolyl, 1,5-pyrindinyl, pyrano[3,4-b]pyrrolyl, isoindazolyl, indoxazinyl, benzoxazolyl, anthranilyl, quinolyl, isoquinolyl, cinnolyl, quinazolyl, naphthyridyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, carbazolyl, xanthenyl, acridinyl, purinyl, thiazolidyl, piperidyl, pyrrolidyl, 1,2-dihydroazinyl, 1,4-dihydroazinyl, 1,2,3,6-tetrahydro-1,3-diazinyl, perhydro-1,4-diazinyl, 1,2-thiapyranyl, and 1,4-thiapyranyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The term "aliphatic heterocylic" includes, 2-isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-dioxinyl, 1,3-dioxinyl, pyrazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiainzyl, 1,2,6-oxathiainzyl, 1,4,2-oxadiainzyl, 1,3,5,2-oxadiainzyl, morpholino, azepinyl, oxepinyl, thiepinyl, 1,2,4-diazepinyl, indoleninyl, 2-isobenzazolyl, 1,2-benzopyranyl, 1,3,2-benzoxazyl, 1,4,2-benzoxazyl, 2,1,3-benzoxazyl, 3,1,4-benzoxazyl, 1,2-benzoisoxazyl, and 1,4-benzoisoxazyl. The term "heterocyclic alkyl" embraces alkyl attached to the heterocyclic. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2-NH_2$). The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes $-(C=O)-$. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is $CH_3-(C=O)-$. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3CO-C=O)-$ and $-(O=)C-OCH_3$. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(CH_3)_3COC(=O)\ (CH_2)_2-$ and $-(CH_2)_2(O=)COCH_3$. The term

"amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an $-C(=NH)-NH_2$ radical. The term "cyanoamidino" denotes an $-C(=N-CN)-NH_2$ radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3-S-). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-S(=O)-$ atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the

residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino ($CH_3C(=O)$–NH–).

[0019] Compounds of Formula I or II would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I or II would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondylo arthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis. Such compounds of Formula I or II would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns, and dermatitis. Compounds of Formula I or II also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I or II would be useful in treating inflammation in such diseases as vascular diseases such as vascularitus, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds of the present invention may also be used for pain. The compounds are useful as antiinflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. The compounds of Formula I or II are useful as agents for treating cancer or anticancer agents. The compounds of Formula I or II may be proapoptotic, antiapoptotic, anticell cycle progressive, antiinvasive, antiproliferative, antiangiogenic, and antimetastatic. The cancer may be colon, ovarian, breast, prostate, gastric, B-cell lymphoma, and multiple myeloma. More specifically, the compounds of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and

skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma. Due to the key role of PKs in the regulation of cellular proliferation, these compounds are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. The compounds of Formula I or II may be used as an anitviral agent. The compounds of this invention are useful as inhibitors of protein kinases. The compounds of this invention are useful as inhibitors of IKK1 and/or IKK2, IKKα/IKKβ heterodimer, TBK or IKK*i*. The compounds of the invention may also useful as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, cyclin dependent kinase (cdk), Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases. The present invention preferably includes compounds, which selectively inhibit IKK2 over IKK1. Preferably, the compounds have an IKK2 IC50 of less than 1 μM, and have a selectivity ratio of IKK2 inhibition over IKK1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have an IKK1 IC50 of greater than 10 μM, and more preferably of greater than 100 μM. The compounds of Formula I or II may also be used to treat angiogenesis associated cardiovascular, ophthalmology and osteoporosis disorders.

The compounds of the present invention may also be used for treatment of knee injury such as sport injuries.

[0020] While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in association with at least one pharmaceutically acceptable carrier, adjuvant, or diluent. The present invention also comprises a method of treating inflammation or inflammation associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorders a therapeutically effective amount of a compound of the present invention. Also included in the family of compounds of the present invention are the pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the present invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, 5-droxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. All of these salts may be prepared by conventional means

from the corresponding compound of the present invention by reacting, for example, the appropriate acid or base with the compound of the present invention.

[0021] Also embraced within this invention are pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and/or excipient (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. Accordingly, the compounds of the present invention may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of the present invention prepared as herein before described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic aqueous solution. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, intravenously, subcutaneously, intramuscularly, intramedullary, orally, or topically. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. The active ingredient may also be administered by injection as a composition wherein, for example, normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution may be used as a suitable carrier. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors,

including the age, weight, sex and medical condition of the sub-ject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg bodyweight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg bodyweight, may be appropriate. The daily dose can be administered in one to four doses per day. For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled release formulation as may be provided in a dispersion of active compound in a sustained release material such as glyceryl monostearate, glyceryl distearate, hydroxypropylmethyl cellulose alone or with a wax. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered orally or filled into a soft gelatin capsule. For rectal administration, the compounds of the present

invention may also be combined with excipients such as cocoa butter, glycerin, gelatin, or polyethylene glycols and molded into a suppository. The methods of the present invention include topical administration of the compounds of the present invention. By topical administration is meant non-systemic administration, including the application of a compound of the invention externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye, and nose, wherein the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal, and intramuscular administration. The amount of a compound of the present invention (hereinafter referred to as the active ingredient) required for therapeutic or prophylactic effect upon topical administration will, of course, vary with the compound chosen, the nature and severity of the condition being treated and the animal undergoing treatment, and is ultimately at the discretion of the physician.

[0022] The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carriers therefore, and optionally any other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.01 to 5.0 wt%. of the formulation.

[0023] Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container, which is then sealed and sterilized by autoclaving, or maintaining at 90-100° C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops

are phenylmercuric nitrate or acetate (0.00217c), benzalkonium chloride (0.0 1%) and chlorhexidine acetate (0.0 1%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol, and propylene glycol.

[0024] Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil. Creams, ointments, or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface-active agent such as an anionic, cationic, or non-ionic surface-active agent such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin may also be included. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

GENERAL SYNTHETIC PROCEDURES

[0025] The starting materials used herein are commercially available or are prepared by routine methods well known to those of ordinary skill in the art and can be found in Scientific Journals and standard reference books, such as the

COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

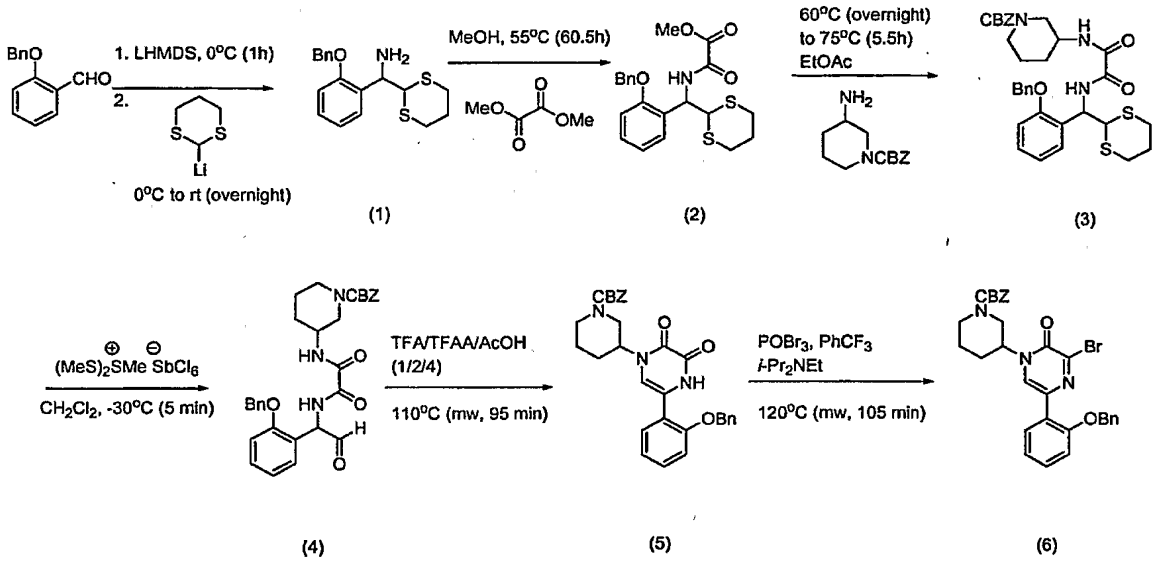
[0026] The compounds of the invention can be synthesized according to the following procedures of Scheme I, II and III, wherein the R substituents are as defined for Formula I -VIII, except where further noted.

The pyrazinone (9) was prepared as outlined in Schemes I and II.

[0027] 2-Benzyloxybenzaldehyde was reacted with lithium bis(trimethylsilyl)amide (LHMDS). The resulting imine was reacted with lithiated 1,3-dithiane to give the amine intermediate (1) upon aqueous quench. Reaction of the amine (1) with dimethyl oxalate gave the amide intermediate (2). Reaction of the intermediate (2) with 1-benzyloxycarbonyl-3-aminopiperidine resulted in the intermediate (3).

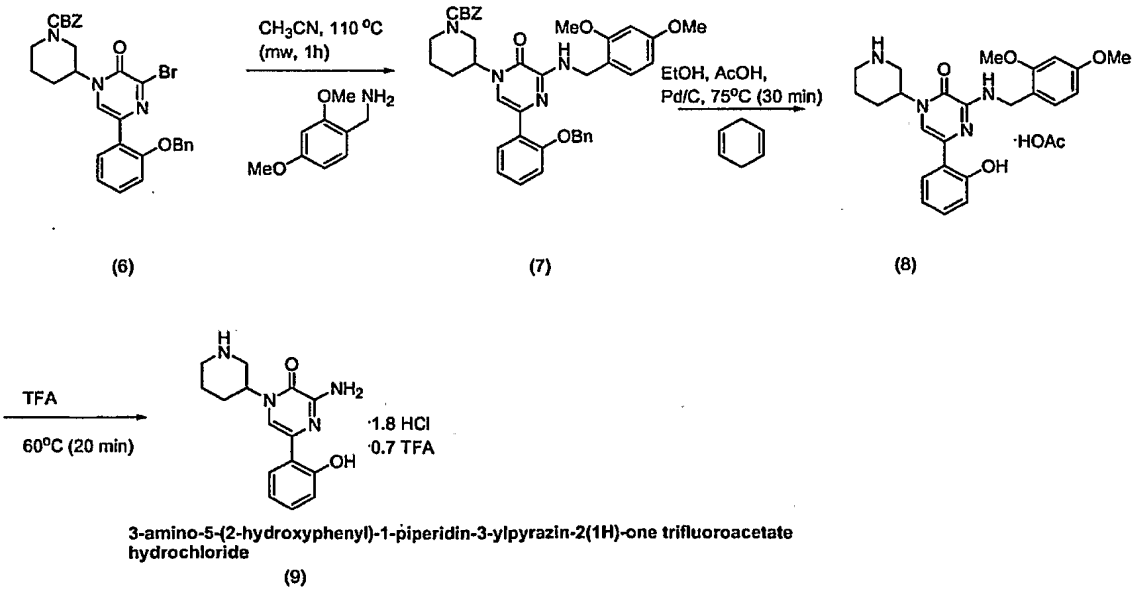
[0028] Deprotection of the dithiane was effected using bis(methylthio)methylsulfonium hexachloroantimonate to give the aldehyde (4). Cyclization to the diketopiperazine (5) was carried out by heating in trifluoroacetic acid, trifluoroacetic anhydride and acetic acid under microwave conditions. The bromide (6) was formed by heating intermediate (5) with phosphoryl bromide and diisopropylethylamine under microwave conditions. The bromide (6) was displaced with 2,4-dimethoxybenzylamine to give the intermediate (7). Partial deprotection was carried out under transfer hydrogenation conditions (ethanol, acetic acid, palladium on carbon, cyclohexadiene) to give intermediate (8). The dimethoxybenzyl protecting group was removed using trifluoroacetic acid. Purification using reverse phase HPLC gave (9) as a mixed hydrochloride/trifluoroacetate salt.

SCHEME I



5

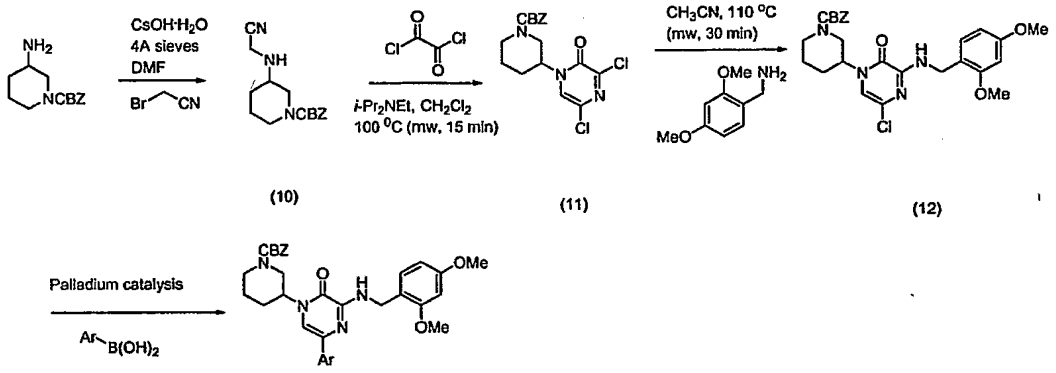
SCHEME II



10 **[0029]** An alternate synthetic approach is outlined in Scheme III.

[0030] Alkylation of 1-benzyloxycarbonyl-3-aminopiperidine with bromoacetonitrile gave compound (10). Reaction with oxalyl choride under microwave conditions gave the dichloropyrazinone (11). Reaction of (11) with 2,4-dimethoxybenzylamine gave the intermediate (12).Coupling of the intermediate (12) with a suitable aromatic boronic acid with palladium catalysis will give an intermediate (13), which is analogous to the intermediate (7) in scheme 2.

SCHEME III

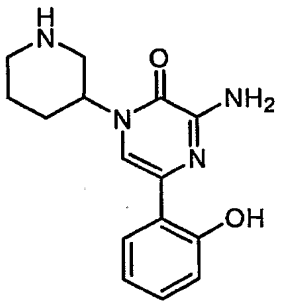


[0031] The complete content of all publications, patents, and patent applications cited in this disclosure are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for the purposes of clarity of understanding, it will be readily apparent to one skilled in the art in light of the teachings of this invention that changes and modifications can be made without departing from the spirit and scope of the present invention. The following examples are provided for exemplification purposes only and are not intended to limit the scope of the invention, which has been described in broad terms above.

EXAMPLES

Example 1

3-amino-5-(2-hydroxyphenyl)-1-piperidin-3-ylpyrazin-2(1H)-one



[0032] To a cooled (0 °C) solution of 1,3-dithiane (1.31 g) in THF (10 mL) was added *n*-BuLi (1.9 M in hexanes, 6.0 mL) slowly by syringe. The resulting mixture was stirred 2 hr at 0°C. In a separate flask, LHMDS (1.0 M in THF, 10 mL) was slowly added to a cooled (0°C) solution of 2-benzyloxybenzaldehyde (2.10g) in THF (20 mL). The resulting solution was stirred 1hr at 0°C. The lithiated dithiane generated above was then added slowly via cannula. The reaction was allowed to warm to room temperature and stir overnight, then quenched by addition of saturated aqueous NH_4Cl. Phases were separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified via flash chromatography (1.5:1 ethyl acetate:hexanes) to give compound **1** as an extremely viscous oil (3.02 g).

[0033] A mixture of compound **1** (2.4 g) and dimethyl oxalate (2.6 g) was heated at 55°C in methanol (50 mL) under N_2 for 60.5 h. The reaction mixture was then diluted with water (50 mL) and the white solid product isolated by vacuum filtration, washing repeatedly with 1:1 methanol:water. Drying in a vacuum oven at 70°C provided compound **2** as a white powdery solid (2.48 g).

[0034] A mixture of compound **2** (2.09 g) and 1-benzyloxycarbonyl-3-aminopiperidine (1.405 g) in ethyl acetate (25 mL) was heated at 60°C overnight then at 75°C for 5.5 h. After cooling to room temperature, the reaction mixture was diluted with hexanes (25 mL) and a white solid isolated by vacuum filtration, washing repeatedly with 1:1 hexanes:ethyl acetate. Owing to the presence of the desired product in the filtrate, the filtrate was concentrated and combined with the

filtered solid. Compound **3** was purified by flash chromatography (20:1 to 10:1 dichloromethane:acetonitrile) to give a white solid (2.24 g).

[0035] To a cooled (-30°C) solution of compound **3** (1.65 g) in dichloromethane (75 mL) was added a solution of methylbis(methylthio) sulfonium hexachloroantimonate (4.56 g) in dichloromethane (50 mL) by cannula over 10 min, maintaining a cooling bath temperature of < -32°C (see Prato, M., et al. (1982) *Synthesis* 679-680). The reaction was stirred 5 min then quenched by pouring onto 1M NaOH (250 mL). The biphasic mixture was diluted with dichloromethane (100 mL) and phases separated. The aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:1 to 5:1 dichloromethane:acetonitrile) to give compound **4** as an off-white solid (1.21 g).

[0036] To a suspension of aldehyde **4** (1.05 g) in acetic acid (16 mL) was added a solution of trifluoroacetic acid:trifluoroacetic anhydride:acetic acid (3.3 mL, 0.6:1.1:4.4). The resulting suspension was heated for 70 minutes in a microwave at 110 °C. An additional 1 mL of the trifluoroacetic acid:trifluoroacetic anhydride:acetic acid solution was added and the mixture heated an additional 25 min at 110 °C in the microwave (see Fleitz, F. J. et al. (2000) *Synth. Commun.* 30, 3171-3180). The reaction mixture was then concentrated under reduced pressure. The crude oil was diluted with a small amount of dichloromethane and treated with pyridine (1 mL). Compound **5** was then isolated by flash chromatography (1.5:1 acetonitrile:dichloromethane) to give a lightly peach-colored foamy solid (0.7534 g).

[0037] To a suspension of compound **5** (0.49 g) and *N,N*-diisopropylethylamine (0.83 mL) in α,α,α-trifluorotoluene (8 mL) under N_2 was added a solution of $POBr_3$ in α,α,α-trifluorotoluene (2 M, 1.3 mL). The resulting mixture was heated 1.75 h at 120°C in the microwave. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (25 mL) and diluted with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (25 mL). Phases were separated and the aqueous phase extracted three times with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Compound **6**

was purified by flash chromatography (2.5:1 to 2:1 hexanes:ethyl acetate) to give a yellow powder (0.175 g).

[0038] A solution of compound **6** (0.1294 g) and 2,4-dimethoxybenzylamine (0.34 mL) in acetonitrile (5 mL) was heated at 110 °C for 1 h in a microwave. Compound **7** was then isolated by flash chromatography (2:1 hexanes:ethyl acetate) to give a lightly yellow solid (0.1282 g).

[0039] To a solution of compound **7** (0.1182 g) and 1,3-cyclohexadiene (0.17 mL) in ethanol:acetic acid (3 mL:0.3 mL) was added Pd/C (0.1115 g, 10 wt. % (dry basis), wet, Degussa type). The resulting heterogeneous mixture was heated to 75°C and stirred vigorously for 30 min. The reaction mixture was then filtered through a plug of celite, washing with ethanol and methanol. Concentration under reduced pressure gave compound **8** as a beige solid (0.0808 g).

[0040] A solution of compound **8** (0.0716 g) in trifluoroacetic acid (18 mL) was heated at 60-69°C for 20 min under N_2 then cooled to room temperature. The reaction was then concentrated under a stream of N_2. Ether was added and then removed under reduced pressure. The resulting solid was triturated with ether and dried. The crude material was purified by reverse-phase HPLC (gradient elution from 1:99 to 50:50 acetonitrile:water, containing trace HCl). Concentration under a stream of N_2 afforded the title compound **9** (3-amino-5-(2-hydroxyphenyl)-1-piperidin-3-ylpyrazin-2(1H)-one) as a mustard-colored fine yellow powder (0.0287 g). The elemental analysis was consistent with a mixed salt containing 1.8 and 0.7 molar equivalents of HCl and trifluoroacetic acid, respectively along with 1.8 H_2O (Calc. C 42.43, H 5.23, N 12.07, Cl 13.75, Found C 42.50, H 5.19, N 11.92, Cl 13.55). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75-2.20 (m, 4H), 2.80-2.94 (m, 1H), 3.24-3.44 (m, 3H), 5.05-5.17 (m, 1H), 6.83-6.92 (m, 2H), 7.16-7.23 (m, 1H), 7.48 (s, 1H), 7.60 (br d, 1H), 7.80-8.50 (br s, 2H), 9.02-9.17 (m, 1H), 9.61 (br d, 1H). m/z = 287.1 (M+1). The IC50 of the titled compound was ≤10 μM in the IKK2 resin assay.

Example 2

Alternative synthesis route

[0041] The title compound of of Example 1 can also prepared using Scheme III as follows:

[0042] A suspension of 1-benzyloxycarbonyl-3-aminopiperidine (1.1 g), 4 Å molecular sieves (3.2 g), and $CsOH \bullet H_2O$ (3.0 g) in DMF (10 mL) was stirred 1 h at room temperature under N_2. Bromoacetonitrile (0.36 mL) was then added by syringe, and the reaction was stirred overnight. Additional bromoacetonitrile (0.35 mL) was then added and the reaction stirred 30 min. The mixture was then diluted with ethyl acetate (75 mL) and filtered. NaOH (1 M, 25 mL), brine (25 mL), and H_2O were added and the phases separated. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with 1 M NaOH and brine, dried with $MgSO_4$, and concentrated under reduced pressure. Compound **10** was purified by flash chromatography to give a brown oil (0.65 g).

[0043] A solution of oxalyl chloride in dichloromethane (2.0 M, 0.60 mL) was added to compound **10** (0.0659 g). *N,N*-diisopropylethylamine (0.1 mL) was added, resulting in some exothermicity and blackening of the reaction mixture. The resulting mixture was heated in a microwave at 100°C for 15 min then concentrated under a stream of N_2 (see Vekemans, J. et al. (1983) *J. Heterocyclic Chem.* 20, 919-923). Compound **11** was then isolated by flash chromatography (20:1 dichloromethane:ethyl acetate) to give a light brown-pink solid (0.050 g).

[0044] A solution of compound **11** (0.0428 g) and 2,4-dimethoxybenzylamine (0.17 mL) in acetonitrile (1 mL) was heated at 110 °C for 30 min in a microwave. The desired product was then isolated by flash chromatography (2:1 hexanes:ethyl acetate) to give compound **12** as a white solid (0.043 g).

BIOLOGICAL EVALUATION

Materials

[0045] SAM$^{2\,TM}$96 Biotin capture plates were from Promega. Anti-FLAG affinity resin, FLAG-peptide, NP-40 (Nonidet P-40), BSA, ATP, ADP, AMP, LPS (*E. coli* serotype 0111:B4), and dithiothreitol were obtained from Sigma Chemicals. Antibodies specific for NEMO (IKKγ) (FL-419), IKK1(H-744), IKK2(H-470) and IκBα(C–21) were purchased from Santa Cruz Biotechnology. Ni-NTA resin was

purchased from Qiagen. Peptides were purchased from American Peptide Company. Protease inhibitor cocktail tablets were from Boehringer Mannheim. Sephacryl S-300 column was from Pharmacia LKB Biotechnology. Centriprep-10 concentrators with a molecular weight cutoff of 10 kDa and membranes with molecular weight cut-off of 30 kDa were obtained from Amicon. [Υ-^{33}P] ATP (2500 Ci/mmol) and [Υ-^{32}P] ATP (6000 Ci/mmol) were purchased from Amersham. The other reagents used were of the highest grade commercially available.

Cloning and Expression

[0046] cDNAs of human IKK1 and IKK2 were amplified by reverse transcriptase-polymerase chain reaction from human placental RNA (Clonetech). hIKK1 was subcloned into pFastBac HTa (Life Technologies) and expressed as N-terminal His_6-tagged fusion protein. The hIKK2 cDNA was amplified using a reverse oligonucleotide primer which incorporated the peptide sequence for a FLAG-epitope tag at the C-terminus of the IKK2 coding region (DYKDDDDKD). The hIKK2:FLAG cDNA was subcloned into the baculovirus vector pFastBac. The rhIKK2 (S177S, E177E) mutant was constructed in the same vector used for wild type rhIKK2 using a QuikChange™ mutagenesis kit (Stratagene). Viral stocks of each construct were used to infect insect cells grown in 40L suspension culture. The cells were lysed at a time that maximal expression and rhIKK activity were demonstrated. Cell lysates were stored at -80 °C until purification of the recombinant proteins was undertaken as described below.

Enzyme Isolation

[0047] All purification procedures were carried out at 4 °C unless otherwise noted. Buffers used are: buffer A: 20 mM Tris-HCl, pH 7.6, containing 50 mM NaCl, 20 mM NaF, 20 mM β-Glycerophosphate, 500 uM sodium orthovanadate, 2.5 mM metabisulfite, 5 mM benzamidine, 1 mM EDTA, 0.5 mM EGTA, 10% glycerol, 1 mM DTT, 1X Complete™ protease inhibitors; buffer B: same as buffer A, except 150 mM NaCl, and buffer C: same as buffer A, except 500 mM NaCl.

Isolation of rhIKK1 homodimer

[0048] Cells from an 8-liter fermentation of baculovirus-expressed IKK1 tagged with His peptide were centrifuged and the cell pellet (MOI 0.1, I=72 hr) was re-suspended in 100 ml of buffer C. The cells were microfluidized and centrifuged at 100,000 X g for 45 min. The supernatant was collected, imidazole added to the final concentration of 10 mM and incubated with 25 ml of Ni-NTA resin for 2 hrs. The suspension was poured into a 25 ml column and washed with 250 ml of buffer C and then with 125 ml of 50 mM imidazole in buffer C. rhIKK1 homodimer was eluted using 300 mM imidazole in buffer C. BSA and NP-40 were added to the enzyme fractions to the final concentration of 0.1 %. The enzyme was dialyzed against buffer B, aliquoted and stored at -80 °C.

Isolation of rhIKK2 homodimer

[0049] A 10-liter culture of baculovirus-expressing IKK2 tagged with FLAG peptide was centrifuged and the cell pellet (MOI=0.1 and I=72 hrs) was re-suspended in buffer A. These cells were microfluidized, and centrifuged at 100,000 X g for 45 min. Supernatant was passed over a G-25 column equilibrated with Buffer A. Protein peak was collected and incubated with anti-FLAG affinity resin on a rotator overnight in buffer B. The resin was washed in batch with 10-15 bed volumes of buffer C. Washed resin was poured into a column and rhIKK2 homodimer was eluted using 5 bed volumes of buffer B containing FLAG peptide. 5 mM DTT, 0.1% NP-40 and BSA (concentrated to 0.1% in final amount) was added to the eluted enzyme before concentrating in using an Amicon membrane with a molecular weight cut-off of 30 kDa. Enzyme was aliquoted and stored at -80 °C.

Isolation of rhIKK1/IKK2 heterodimer

[0050] The heterodimer enzyme was produced by coinfection in a baculovirus system (FLAG IKK2/IKK1 His; MOI=0.1 and I=72 hrs). Infected cells were centrifuged and the cell pellet (10.0 g) was suspended in 50 ml of buffer A. The protein suspension was microfluidized and centrifuged at 100,000 X g for 45 min. Imidazole was added to the supernatant to a final concentration of 10 mM. The protein was allowed to bind 25 ml of Ni-NTA resin by mixing for 2 hrs. The

protein-resin slurry was poured into a 25 ml column and washed with 250 ml of buffer A containing 10 mM imidazole followed by 125 ml of buffer A containing 50 mM imidazole. Buffer A, containing 300 mM imidazole, was then used to elute the protein. A 75 ml pool was collected and NP-40 was added to a final concentration of 0.1%. The protein solution was then dialyzed against buffer B. The dialyzed heterodimer enzyme was then allowed to bind to 25 ml of anti-FLAG M2 agarose affinity gel overnight with constant mixing. The protein-resin slurry was then centrifuged for 5 min at 2,000 rpm. The supernatant was collected and the resin re-suspended in 100 ml of buffer C containing 0.1% NP-40. The resin was washed with 375 ml of buffer C containing 0.1 % NP-40. The protein-resin was poured into a 25 ml column and the enzyme eluted using buffer B containing FLAG peptide. Enzyme fractions (100 ml) were collected and concentrated to 20 ml using an Amicon membrane with molecular weight cut-off of 30 kDa. Bovine serum albumin was added to the concentrated enzyme to final concentration of 0.1 %. The enzyme was then aliquoted and stored at -80 °C.

Cell Culture

[0051] The wild type (wt) human pre-B cell line, 70Z/3, and its mutant, 1.3E2, were generously provided by Dr. Carol Sibley. Wt 70Z/3 and 1.3E2 cells were grown in RPMI 1640 (Gibco) supplemented with 7 % defined bovine serum (Hyclone) and 50 μM 2-mercaptoethanol. Human monocytic leukemia THP-1 cells, obtained from ATCC, were cultured in RPMI 1640 supplemented with 10% defined bovine serum, 10 mM HEPES, 1.0 mM sodium pyruvate and 50 μM 2-mercaptoethanol. For experiments, cells were plated in 6 well plates at $1x10^6$ cells/ml in fresh media. Pre-B cells were stimulated by the addition of 10 μg/ml LPS for varying lengths of time ranging from 0-4 hr. THP-1 cells were stimulated by the addition of 1 μg/ml LPS for 45 minutes. Cells were pelleted, washed with cold 50 mM sodium phosphate buffer, pH 7.4 containing 0.15 M NaCl and lysed at 4 °C in 20 mM Hepes buffer, pH 7.6 containing 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM sodium orthovanadate, 10 mM β-glycerophosphate, 1 mM NaF, 1 mM PMSF, 1 mM DTT and 0.5 % NP40 (lysis buffer). The cytosolic fractions obtained following centrifugation at 10,000 X g were stored at -80° C until used.

Immunoprecipitation and Western Blotting

[0052] SF9 cells paste containing rhIKKs were centrifuged (100,000 X g, 10 min) to remove debris. rhIKKs were immunoprecipitated (100 μg of cell paste) from the cell supernatant using 3 μg of anti-NEMO antibody (FL-419), followed by coupling to protein A sepharose beads. rhIKKs were also immunoprecipitated from affinity chromatography purified protein preparations (1 μg) using anti-FLAG, anti-His or anti-NEMO antibodies (1-4 μg) followed by protein A sepharose coupling. The native, human IKK complex was immunoprecipitated from THP-1 cell homogenates (300 μg/condition) using the anti-NEMO antibody. Immune complexes were pelleted and washed 3 times with 1 ml cold lysis buffer. Immunoprecipitated rhIKKs were chromatographed by SDS-PAGE (8% Tris-glycine) and transferred to nitrocellulose membranes (Novex) and detected by chemiluminescense (SuperSignal) using specific anti-IKK antibodies (IKK2 H-470, IKK1 H-744). Native IKK2, IκBα, and NEMO proteins from cytosolic lysates (20-80 μg) were separated by SDS-PAGE and visualized by chemiluminescense using specific antibodies.

Phosphatase Treatment

[0053] Immunoprecipitated rhIKKs were washed 2 times in 50 mM Tris-HCl, pH 8.2 containing 0.1 mM EDTA, 1 mM DTT, 1 mM PMSF and 2 mM $MnCl_2$ and resuspended in 50 μl. Phosphatase (λPPase, 1000 U) was pre-diluted in the same buffer and added to the IKK samples. Following incubation at room temperature for 30 minutes with intermittent mixing, cold lysis buffer was added to the tubes to stop the reaction. After several washes, 10 % of the beads were removed for Western analysis, and the remaining material was pelleted and resuspended in 100 μl of the buffer used for the *in vitro* kinase assay.

IKKα SAM Enzyme Assay

[0054] IKKα kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu), a SAM$^{2\,TM}$ 96 Biotin capture plate and a vacuum system. The standard reaction mixture contained 5 μM biotinylated IκBα peptide, 1 μM [γ-^{33}P] ATP (about 1 X 10^5 cpm), 1 mM DTT, 50 mM KCl, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 10 mM NaF, 25 mM Hepes buffer, pH. 7.6 and enzyme solution (1-10 μl) in a final volume of 50 μl. After incubation at 25 °C for 30 min, 25 μl of the reaction mixture was withdrawn and added to a SAM$^{2\,TM}$ 96 Biotin capture 96-well plate. Each well was then washed successively with 800 μl 2 M NaCl, 1.2 ml of NaCl containing 1% H_3PO_4, 400 μl H_2O, and 200 μl 95% ethanol. The plate was allowed to dry in a hood at 25 °C for 1 hr and then 25 μl of scintillation fluid (Microscint 20) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard). Under each assay condition, the degree of phosphorylation of IκBα peptide substrate was linear with time and concentration for all purified enzymes. Results from the biotinylated peptide assay were confirmed by SDS-PAGE analysis of kinase reaction utilizing a GST-$IκBα_{1-54}$ and [γ-^{32}P] ATP. The resulting radiolabeled substrate was quantitated by Phosphoimager (Molecular Dynamics). An ion exchange resin assay was also employed using [γ-^{33}P] ATP and GST-$IκBα_{1-54}$ fusion protein as the substrates. Each assay system yielded consistent results in regard to K_m and specific activities for each of the purified kinase isoforms. One unit of enzyme activity was defined as the amount required to catalyze the transfer of 1 nmole of phosphate from ATP to IκBα peptide per min. Specific activity was expressed as units per mg of protein. For experiments related to K_m determination of purified enzymes, various concentrations of ATP or IκBα peptide were used in the assay at either a fixed IκBα or ATP concentration. For IκBα peptide K_m, assays were carried out with 0.1 μg of enzyme, 5 μM ATP and IκBα peptide from 0.5 to 20 μM. For ATP K_m, assays were carried out with 0.1 μg of enzyme, 10 μM IκBα peptide and ATP from 0.1 to 10 μM. For K_m determination of rhIKK1 homodimer, due to its low activity and higher K_m for IκBα peptide, rhIKK1 homodimer (0.3 μg) was assayed with 125 μM IκBα peptide and a 5-fold higher specific activity of ATP (from 0.1 to 10 μM)

for ATP K_m experiments and a 5-fold higher specific activity of 5 μM ATP and IκBα peptide (from 5 to 200 μM) for IκBα peptide K_m experiments.

IKKβ Resin Enzyme Assay

[0055] IKKβ kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 ul inhibitor in a final volume of 50 μl. After incubation at 25 °C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

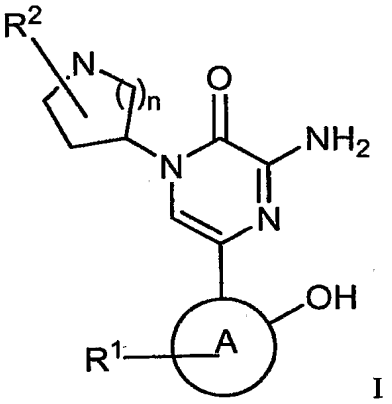
IKK heterodimer Resin Enzyme Assay

[0056] IKK heterodimer kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 μl inhibitor in a final volume of 50 μl. After incubation at 25 °C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each

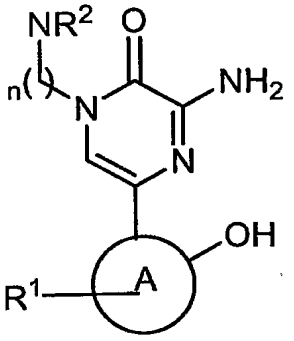
well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

WHAT IS CLAIMED IS

1. The compound of Formula I or II



I



II

wherein

n is 1, 2, or 3

A is a 3 to 12 membered fused or unfused heteroaryl or aryl, optionally saturated, and optionally substituted with one or more R^1 group;

R^1 is independently selected from the group consisting of: hydrido, halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, cycloalkyl, cycloalkylalkyl, heteroaryl, alkenyl, OR^3, $(CH_2)_mOR^3$ wherein m is 1, 2, or 3, $(CH_2)_pCO_2R^3$ wherein p is 1, or 2, SR^4, $SO_2N(R^4)\ R^{4'}$, NHR^5, $NHCOR^5$, NR^5COR^5, $NHCO(OR^5)$, $NR^5CO(OR^5)$, $NR^5SO_2R^6$, $NHSO_2N(R^6)R^{6'}$, $NR^5CON(R^6)R^{6'}$, COR^5, CO_2R^4, $CON(R^4)\ R^{4'}$, wherein R^4 and $R^{4'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, wherein R^6 and $R^{6'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, and wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^5;

R^2 is one or more substituent independently selected from the group consisting of: hydrido, halogen, alkylsulfinyl, alkylsulfonyl, cyano,

alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, alkenyl, OR^3, SR^4, $SO_2N(R^4)R^{4'}$, NHR^5, $NHCOR^5$, NR^5COR^5, $NHCO(OR^5)$, $NR^5CO(OR^5)$, $NR^5SO_2R^6$, $NHSO_2N(R^6)R^{6'}$, $NR^5CON(R^6)R^{6'}$, COR^5, CO_2R^4, $CON(R^4)R^{4'}$, wherein R^4 and $R^{4'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, wherein R^6 and $R^{6'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^5, and wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^5;

R^3 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, heteroarylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, heterocyclic, cycloalkyl, cycloalkylalkyl, arylalkyl, and arylalkylamino wherein said aryl is optionally substituted wit one or more radical selected from the group consisting of lower alkyl, aminoalkyl, alkoxy and halogen;

R^4 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, heteroarylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, heterocyclic, cycloalkyl, cycloalkylalkyl, arylalkyl, and arylalkylamino wherein said aryl is optionally substituted wit one or more radical selected from the group consisting of lower alkyl, aminoalkyl, alkoxy and halogen;

$R^{4'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, heteroarylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, heterocyclic, cycloalkyl, cycloalkylalkyl, arylalkyl, and arylalkylamino wherein said aryl is optionally substituted wit one or more radical selected from the group consisting of lower alkyl, aminoalkyl, alkoxy and halogen;

R^5 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

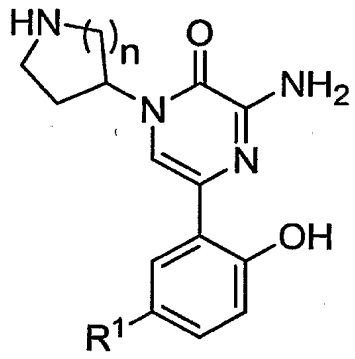
R^6 is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic; and

$R^{6'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

or isomers, tautomers, polymorphs, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein said compound is of Formula I.

3. The compound of claim 2 wherein said compound is of Formula III



III

wherein

n is 1, 2, or 3;

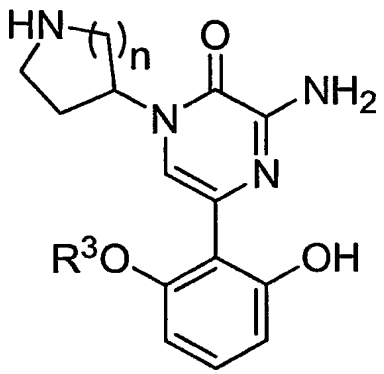
$\mathbf{R^1}$ is selected from the group consisiting of hydrido, OR^3, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, and heterocyclic; and

$\mathbf{R^3}$ is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl.

4. The compound of claim 3 selected from the group consisting of

3-amino-5-(2-hydroxyphenyl)-1-piperidin-3-ylpyrazin-2(1H)-one trifluoroacetate hydrochloride.

5. The compound of claim 2 of Formula V



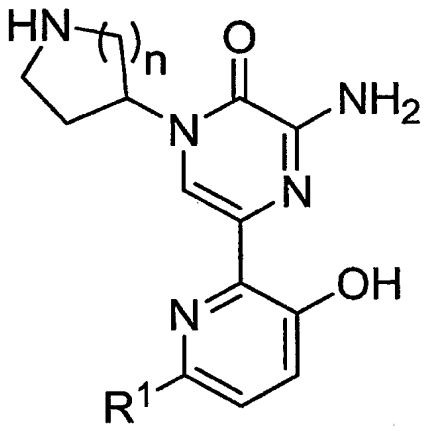
V

wherein

n is 1, 2, or 3; and

R^3 is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, CH_2C_3-C_7cycloalkyl, and benzyl.

6. The compound of claim 2 of the Formula VI



VI

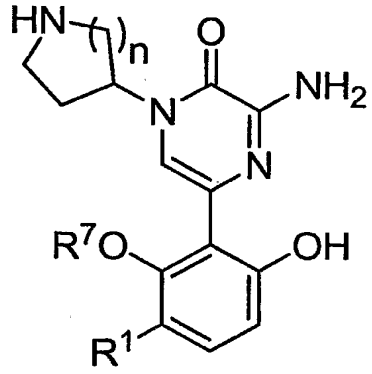
wherein

n is 1, 2, or 3;

R^1 is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, OR^3 and heterocyclic; and

R^3 is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl.

7. The compound of claim 1 of formula VII



VII

wherein

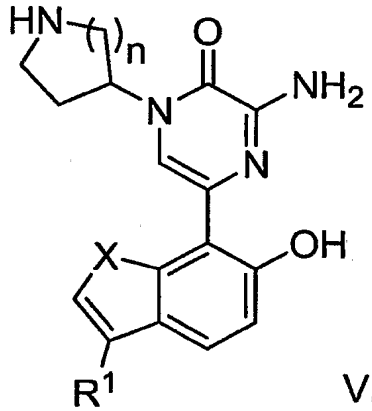
n is 1, 2, or 3;

$\mathbf{R^1}$ is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, OR^3 and heterocyclic;

$\mathbf{R^3}$ is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl; and

$\mathbf{R^7}$ is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and benzyl.

8. The compound of claim 1 of formula VIII



VIII

wherein

n is 1, 2, or 3;

X is S or O;

$\mathbf{R^1}$ is $(CH_2)_mOR^3$ or $(CH_2)_pCO_2R^3$;

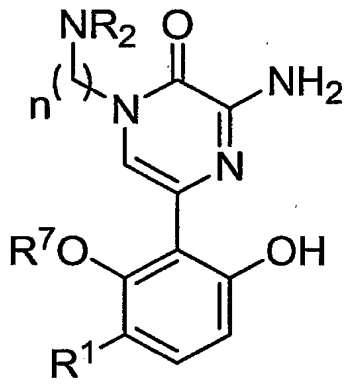
m is 1, 2, or 3;

p is 0, 1, or 2; and

$\mathbf{R^3}$ is hydrido or C_1-C_6 alkyl.

9. The compound of claim 1 wherein said compound is of formula II.

10. The compound of claim 9 of formula IV



IV

wherein

n is 1, 2, or 3;

$\mathbf{R^2}$ is hydrido or lower alkyl;

$\mathbf{R^1}$ is selected from the group consisiting of hydrido, C_1-C_6 alkyl, C_5-C_7 cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, aryl, halogen, OR^3 and heterocyclic;

$\mathbf{R^3}$ is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7cycloalkyl, benzyl, CH_2C_3-C_7cycloalkyl, and aryl; and

$\mathbf{R^7}$ is selected from the group consisting of C_1-C_6 alkyl, C_5-C_7cycloalkyl, CH_2C_3-C_7cycloalkyl, and benzyl.

11. A composition comprising the compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 and at least one pharmaceutically acceptable carrier.

12. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10,.

13. The method of claim 12 for use in the treatment of cancer.

14. The method of claim 12 for use in the treatment of inflammation.

15. The method of claim 12 for use in the treatment of an inflammation-associated disorder.

16. The method of claim 15 wherein the inflammation-associated disorder is arthritis.

17. The method of claim 15 wherein the inflammation-associated disorder is pain

18. The method of claim 15 wherein the inflammation-associated disorder is fever.

ABSTRACT

The present invention relates to substituted pyrazinone derivatives, compositions comprising such, intermediates, methods of making substituted pyrazinone derivatives, and methods for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

CERTIFICATE OF MAILING BY EXPRESS MAIL (37 CFR 1.8)

Serial No: Not Assigned
Filing Date: August 27, 2003
Group Art Unit: Not Assigned
Docket No: 01710/1/PR

Invention: Substituted Pyrazinone Compounds for the Treatment of Inflammation

Date of Deposit: October 14, 2003

I hereby certify that these papers or fee is being deposited with the United States Post Office to Addressee service under 37 CFR 1.10 & 1.8 on the date indicated above and is addressed to Mail Stop New Application, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450:

Fee Transmittal
Provisional Application for Patent Cover Sheet
Abstract
Application (pages 1-47)
Assignment Cover Sheet
Assignment
Return Postcard

Linda Haley
(Typed or printed name of person mailing paper or fee)

Linda Haley
(Signature of person mailing paper or fee)

EXPRESS MAIL LABEL NO: EV 325048299 US